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(54) Title: METHODS OF TREATING THE SYMPTOMS OF ATROPHIC VAGINITIS AND ALTERED SEXUAL BEHAVIOR IN POSTMENOPAUSAL WOMEN

(57) Abstract

A novel method for treating the symptoms of atrophic vaginitis and altered sexual behavior in postmenopausal women is described.

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# METHODS OF TREATING THE SYMPTOMS OF ATROPHIC VAGINITIS AND ALTERED SEXUAL BEHAVIOR IN POSTMENOPAUSAL WOMEN

## Field of the Invention

The present invention relates to therapeutic agents that bind to the estrogen receptor and cause tissue specific estogen agonist effects, that have been found to be useful in the treatment of the symptoms of atrophic vaginitis and altered sexual behavior in postmenopausal women.

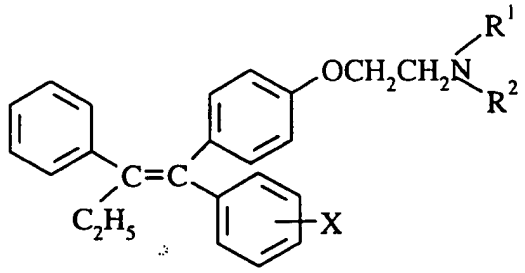
## Background of the Invention

Menopause and the perimenopause in women (also known as the climacteric) are often marked by the occurrence of symptoms relating to loss of estrogen stimulated vaginal secretions (atrophic vaginitis). Alterations in sexual behavior are also common at the time of the menopause. The standard treatment for these symptoms is hormone replacement therapy (HRT) which may be given topically for the relief of vaginal symptoms. This use of HRT is not without controversy. Questions have arisen as to whether estrogen replacement should be continued beyond one to two years. There appears to be an increased risk of breast and endometrial cancer with the long term use of estrogen replacement therapy. Additionally, short term side-effects of HRT include weight gain, breast tenderness and vaginal bleeding. For a more detailed discussion of the effects of HRT see Valda et al. (1994). Hormonal Treatment for the Climacteric: Alleviation of Symptoms and Prevention of Postmenopausal Disease, The Lancet, vol. 343, pages 654-658.

## Summary of the Invention

This invention provides a method for the prevention and treatment of the symptoms of atrophic vaginitis and altered sexual behavior in postmenopausal women without the side effects of Hormonal Replacement Therapy (HRT). The method comprises administering to a human in need thereof an effective amount of a therapeutic agent that binds to the estrogen receptor and produces a tissue specific estrogen agonist effect in the vaginal and cervical glandular/epithelial cells or the specific areas of the brain that control sexual

behavior. Specifically, compounds that can be utilized in this invention are compounds of formula I



(I)

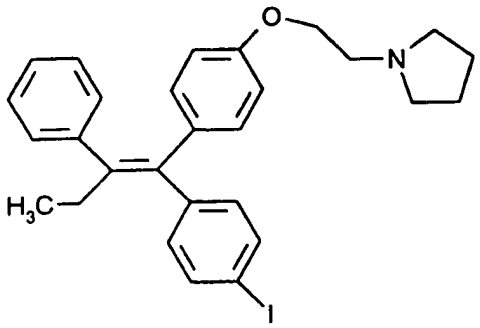
wherein X represents 3- or 4- iodo or bromo and the $R^1$ and $R^2$ symbols, which may be the same or different, represent $C_{1-3}$ alkyl, especially methyl or ethyl, groups or $R^1$ represents a hydrogen atom and $R^2$ a $C_{1-3}$ alkyl group or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached represent a saturated heterocyclic group, typically having 5 or 6 ring atoms, especially a pyrrolidino, piperidino, 4-methylpiperidino or morpholino group, and their pharmaceutically acceptable acid addition salts. Preferred is the compound known as idoxifene.

Detailed Description of the Invention

The present invention is a therapeutic method for treating the symptoms of atrophic vaginitis and altered sexual behavior in postmenopausal women with agents that bind to the estrogen receptor and, as a consequence of that interaction with the estrogen receptor, cause either estrogenic (estrogen agonist) or antiestrogenic (estrogen antagonist) effects in different tissues. Thus the same agent may be estrogenic in one tissue but antiestrogenic in another. Some compounds of this description are in clinical use because of the beneficial effects that are produced in specific tissues as a result of binding to the estrogen receptor (for example the use of the antiestrogenic effects of tamoxifen in breast tissue to provide therapeutic benefit in the treatment of breast cancer). The preferred effect of a compound for the desired method of treatment is to produce estrogenic effects in the vaginal epithelial and cervical glandular cells or the specific areas of the brain that control sexual behavior. This would have the clinical effect of reducing the severity of vaginal itching and dryness, pain on sexual intercourse and decreased libido by having the same effect as estrogen in

these tissues. An example of such a compound is idoxifene. Preferred compounds are described in formula I above and in U.S. patent 4,839,155.

The preferred compound for the described method of treatment is




(E)-1-[2-[4-[1-(4-Iodophenyl)-2-phenyl-1-butenyl]phenoxy]pyrrolidine

(Idoxifene)

The symptoms that would be treated in this invention are an important component of a menopausal syndrome that also includes vasomotor symptoms (hot flashes), sleep disturbance, agitation, nervousness, mood changes, anxiety, irritability, loss of memory and concentration, crying spells, tiredness, depression, headache, and joint or muscle pain. For a more detailed discussion of this phenomenom, please see Oldenhave A., Jaszman LJB, Haspels AA, Everaerd W Th AM, Impact of climacteric on well-being, Am J Obstet Gynecol, 1993; 168: 772-80. The cause of the increase in symptoms of atrophic vaginitis at the time of the menopause is the loss of estrogen (as a result of ovarian failure) which causes the mucus producing cells of the vaginal epithelium and cervix to become atrophic. This effects may last for many years after the menopause. Additionally the lack of estrogen affects the function of the areas of the brain that control sexual behavior. Thus many patients experience a decrease in libido at the time of the menopause.

In a study in ovariectomized cynomologous monkeys idoxifene caused a dose related protection from the loss of vaginal epithelial stratification/cornification and cervical mucus secretion that was observed in the ovariectomized control animals.

A double-blind placebo controlled trial of three doses of Idoxifene (tablet strengths were 2.5, 5.0 and 10 mgs) given daily for four weeks was performed to test the effect of idoxifene in patients with moderate or severe vasomotor symptoms. A questionaire was also administered to the patients to provide information about the severity of the other

symptoms that comprise the menopausal syndrome including those that would be treated in this invention. A loading dose regimen was employed which involved taking three tablets as a single daily dose for the first week and one tablet per day thereafter. Analysis of the data from the patient questionaire revealed that the responses to the questions on sexual function were significantly improved from baseline in the group of patients who received 5mg/day of idoxifene.

The data from the above analysis were as follows:

| Placebo (n= 40) | 5.0 mg/day (n= 39) |
|---|---|
| 22.2% | 34.2% |

The above figures represent the percentage improvement in the scores of response to the specific questions relationg to sexual function compared to responses to the same questions before treatment. The differences from baseline were statistically significant ($p<0.05$).

In a second study testing three months of treatment with the same doses of idoxifene in postmenopausal women the percentage of subjects reporting leukorrhoea, indicating a return of physiological vaginal secretions, was as follows:

| Placebo | 2.5mg/day | 5.0mg/day | 10.0mg/day |
|---|---|---|---|
| 4% | 24% | 12% | 17% |

The compounds of the instant invention and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example, polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or coloring agent.

A composition in the form of a tablet can be prepared using any suitable pharmacuetical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

The compounds of the instant invention and their pharmaceutically acceptable salts which are active when administered parenterally (i.e. by injection of infusion) can be formulated as solutions or suspensions.

A composition for parenteral administration will generally consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository composition comprises a compound of the instant invention or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or coca butter or other low melting vegetable or synthetic waxes or fats.

A typical transdermal formulation comprises a conventional aqueous or non-aqueous vehicle, for example, a cream, ointment lotion or paste or in the form of a medicated plaster, patch or membrane.

For topical administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting and bodying agents, as for example, polyethylene glycols; antibacterial components such as quaternary ammonium compounds; buffering ingredients such as alkali metal chloride; antioxidants such as sodium metabisulfite; and other conventional ingredients such as sorbitan monolaurate.

Preferably the composition is in unit dose form. Doses of the compounds of the instant invention in a pharmaceutical dosage unit will be an efficiacious, non-toxic quantity

selected from the range of .01 - 200 mg/kg of active compound, preferably .1 - 100 mg/kg. The selected dose is administered to a human patient in need of treatment for vasomotor symptoms from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 10 to 500 mg of active compound. Lower dosages are used generally for parenteral administration. Oral administration is used when safe, effective, and convenient for the patient.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

Example 1

An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

| Ingredients | Amounts |
|---|---|
| (E)-1-[2-[4-[1-(4-Iodophenyl)-2-phenyl-1-butenyl] phenoxy]pyrrolidine | 100 mg |
| magnesium stearate | 10 mg |
| lactose | 100 mg |

Example 2

The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelating solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

| Ingredients | Amounts |
|---|---|
| (E)-1-[2-[4-[1-(4-Iodophenyl)-2-phenyl-1-butenyl] phenoxy]pyrrolidine | 75 mg |
| calcium sulfate dihydrate | 100 mg |
| sucrose | 15 mg |
| starch | 8 mg |
| talc | 4 mg |
| stearic acid | 2 mg |

Example 3

(E)-1-[2-[4-[1-(4-Iodophenyl)-2-phenyl-1-butenyl]phenoxy]pyrrolidine, 50 mg, is dispersed in 25 ml of normal saline to prepare an injectable preparation.

What is claimed is:

1. A method of treating the symptoms of atrophic vaginitis and altered sexual behavior in postmenopausal women which comprises administering to a subject in need thereof an effective amount of a compound of formula I.

2. A method according to Claim 1 wherein the compound of formula I is (E)-1-[2-[4-[1-(4-Iodophenyl)-2-phenyl-1-butenyl]phenoxy]ethyl]pyrrolidine.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13460

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 43/40
US CL :514/317, 315
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317, 315

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5,472,985 A (GRAINGER et al.) 05 December 1995, see entire document. | 1 and 2 |
| A | US 4,839,155 A (MCCAGUE) 13 June 1989, see entire document. | 1 and 2 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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26 AUGUST 1998

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REGISTRY, WPIDS, HCAPLUS, HCAOLD, EMBASE, MEDLINE, USPATFULL structure search with the following terms: disease or reperfusion, smithkline, idoxifen? or SB223030, ?menopaus? or cognit? or ?vagin? or behav?